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Abstract: OBJECTIVES Data from randomized controlled trials have shown the feasibility of discontinuation of bDMARD therapy in patients with RA that have reached remission. Criteria for selecting patients that are likely to remain in remission are still incompletely defined.We aimed to identify predictors of successful discontinuation of bDMARD therapy in the Swiss Clinical Quality Management (SCQM) registry, a real-world cohort of RA patients. METHODS RA patients in DAS28-ESR remission who stopped bDMARD/tsDMARD treatment were included. Loss of remission was defined as a DAS28-ESR $>$ 2.6 or restart of a bDMARD/tsDMARD. Time to loss of remission was the main outcome. Kaplan-Meier methods were applied and cox regression was used for multivariable analyses adjusting for confounding factors. Missing data were imputed using multiple imputation. RESULTS 318 patients in a bDMARD/tsDMARD-free remission were followed between 1997 and 2017. 241 patients (76%) lost remission after a median time of 0.9 years (95%CI 0.7-1.0). The time to loss of remission was shorter in women, in patients with a longer disease duration >4yrs and in patients who did not meet CDAI remission criteria at baseline. Remission was longer in patients with csDMARD therapy during b/tsDMARD free remission (HR 0.8, p= 0.05, 95%CI 0.6-1.0). CONCLUSION In a real-world patient population the majority of patients who discontinued b/tsDMARD treatment lost remission within <1 year. Our study confirms that fulfilment of more rigorous remission criteria and csDMARD treatment increases the chance of maintaining b/tsDMARD free remission.

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Abstract

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We aimed to identify predictors of successful discontinuation of bDMARD therapy in the Swiss Clinical Quality Management (SCQM) registry, a real-world cohort of RA patients.

Methods: RA patients in DAS28-ESR remission who stopped bDMARD/tsDMARD treatment were included. Loss of remission was defined as a DAS28-ESR>2.6 or restart of a bDMARD/tsDMARD. Time to loss of remission was the main outcome. Kaplan-Meier methods were applied and cox regression was used for multivariable analyses adjusting for confounding factors. Missing data were imputed using multiple imputation.

Results: 318 patients in a bDMARD/tsDMARD-free remission were followed between 1997 and 2017. 241 patients (76%) lost remission after a median time of 0.9 years (95%CI 0.7-1.0). The time to loss of remission was shorter in women, in patients with a longer disease duration >4yrs and in patients who did not meet CDAI remission criteria at baseline. Remission was longer in patients with csDMARD therapy during b/tsDMARD free remission (HR 0.8, p=0.05, 95%CI 0.6-1.0).

Conclusion: In a real-world patient population the majority of patients who discontinued b/tsDMARD treatment lost remission within less than 1 year. Our study confirms that fulfilment of more rigorous remission criteria and csDMARD treatment increases the chance of maintaining b/tsDMARD free remission.

Key words: Rheumatoid arthritis, remission, bDMARD therapy, bDMARD discontinuation, predictors

Key messages:

- Remission is lost in RA patients less than one year after discontinuation of bDMARD/tsDMARD therapy.
- Discontinuation of bDMARD/tsDMARD treatment should be considered for patients with short disease duration who fulfil stringent CDAI remission criteria.
- Maintenance of csDMARDs increases the duration of remission without bDMARD/tsDMARDs.

Introduction

Early treatment with tight control and treat-to-target approaches and the introduction of biologic disease modifying anti-rheumatic drugs (bDMARD) substantially improved the therapeutic options in RA. Combination therapy of bDMARD with methotrexate was shown to potently suppress inflammation and erosive joint destruction and remission became achievable in up to 75% of patients (1). With an increasing population of patients in long-term remission, tapering or discontinuing DMARD therapy, in particular biologics, has become a focus of clinical research in RA. In patients with sustained remission bDMARD tapering is proposed by the current EULAR and ACR recommendations (2, 3) in order to minimize the risk of side effects and for economic reasons (4-6). Data from randomized controlled trials have shown that in patients with sustained remission tapering of DMARD therapy is feasible (7), however discontinuation of bDMARDs was associated with an increased risk of losing remission or low disease activity (LDA, defined as DAS28-ESR ≥2.6 and ≤3.2) and radiographic progression (8). Nevertheless, an important percentage of patients retained remission after discontinuation of biologics in randomized controlled trials. Several studies have reported factors predicting maintenance of remission after discontinuation of bDMARD. In a recent systematic literature review low disease activity, better physical function, absence of rheumatoid factor and ACPA and low CRP/ESR were described, however due to a great heterogeneity of the studies no firm conclusions could be drawn (9). Thus, there is still uncertainty how to select patients for successful

discontinuation of bDMARDs. In particular, there is a lack of observational data from large patient cohorts with longer follow up. We therefore aimed to analyse patients in remission in a large prospective cohort study under real-world conditions, to define predictors for maintenance of remission after discontinuation of bDMARD or targeted synthetic DMARD (tsDMARDs).

Methods

Study design and patients

This study is based on the multicenter, longitudinal RA cohort of the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM-RA). SCQM-RA has been described in detail previously (10). Patients included in the registry are evaluated at regular intervals for disease activity, patient reported outcomes and DMARD therapy. All patients enrolled in SCQM have provided a written informed consent. The study was approved by the responsible ethics review board, EKNZ (2020-00018).

In this analysis, we included patients with RA, as diagnosed by the treating rheumatologist, who had stopped treatment with a bDMARD or tsDMARD between June 2001 and December 2017 and were thereafter in remission. For simplicity bDMARDs and tsDMARDs are referred to as bDMARDs. Remission was defined by a disease activity score based on 28 joints using the erythrocyte sedimentation rate (DAS28-ESR) below or equal to 2.6. To be included in this study, patients were required to have a clinical visit with a DAS28-ESR≤2.6 within a period of 90 days before, or 30 days after bDMARD discontinuation and at least one follow-up visit after the stop of the bDMARD.

Patients on rituximab were excluded because of the long and varying dosing intervals, which do not allow to define bDMARD free remission time. We did, however, include patients on tsDMARDs because of their efficacy profile comparable to bDMARDs (only tofacitinib being approved in Switzerland during the study period).

To exclude patients with short interruptions of therapy for other reasons, we defined a minimal time after discontinuation of the bDMARD until a visit with a DAS28-ESR flare or reintroduction of a bDMARD. The definition of this minimal period was determined as multiples of the dosing interval of each bDMARD. For abatacept and tocilizumab we defined this period to be 60 days for i.v. and 30 days for s.c. administration, for adalimumab and certolizumab 42 days, for etanercept 30 days, for golimumab 60 days, for infliximab 90 days and for tofacitinib 14 days.

Conventional synthetic DMARD (csDMARD) was defined as therapy with methotrexate or leflunomide. Concomitant treatment with hydroxychloroquine (n=5) or sulfasalazine (n=6) alone, or

hydroxychloroquine and sulfasalazine combination (n=2) was not considered as csDMARD therapy for our analysis.

Patients were included regardless of the reason for discontinuation of the bDMARD recorded in the databank. Remission was indicated as reason for discontinuation in 28%, adverse events in 27% and ineffectiveness of bDMARD in 15%, for 10% of patients the reason was missing. To exclude the possibility, that patients could have been misclassified by our selection criteria, we also analyzed a population that excluded all patients for whom insufficient treatment response had been indicated as a reason for discontinuation of bDMARD treatment.

Outcomes

The main outcome of this study was the time between discontinuation of the bDMARD and the loss of remission. Loss of remission was defined as either a DAS28-ESR above 2.6 or the reintroduction of therapy with a bDMARD. Time in remission was defined as the time between the stop of the bDMARD of interest until loss of remission or until the patient was censored (at the last visit in SCQM).

Explanatory variables

The association of patient characteristics and disease related factors at the time of bDMARD discontinuation ("baseline") with the time in bDMARD-free remission was analysed. We analysed the following patient characteristics and disease related factors: age and smoking status, disease duration defined as the time from the first symptoms to inclusion in the study, the presence of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) , disease activity as measured by DAS28-ESR, clinical disease activity index (CDAI), simplified disease activity index (SDAI) and RA disease activity index (RADAI5), health assessment questionnaire (HAQ) score, concomitant treatment with methotrexate or leflunomide (csDMARD) at any time during bDMARD-free remission, the number of previous bDMARDs, and the type of bDMARD prior to its discontinuation.

Statistical Methods

Frequencies/percentages or median/interquartile ranges (IQR) were calculated. Kaplan-Meier methods were applied to univariately assess associations of patient characteristics and disease related factors with the time in remission after bDMARD discontinuation.

Cox proportional hazards regression analysis was applied to multivariably combine the *a priori* defined possible risk factors of loss of remission. The disease related factors as described above were included in the multivariable model. Missing baseline values were imputed using multiple imputation with chained equations (*m* = 50) using Stata's inbuilt *mi* command. Continuous data were modelled using predictive mean matching and categorical data were modelled by logistic regression in the imputation model (11-13). For composite scores such as the DAS28-ESR, CDAI and SDAI the components of the scores were imputed. All (multivariable) regression results in this paper are based on the imputed data (the results obtained from the complete case analyses are provided as supplementary material). All analyses were performed with Stata/IC 14.2 (StataCorp, College Station, TX, USA).

Results

Of the total 9625 RA patients in the SCQM registry, 318 patients fulfilled the inclusion criteria. Of these 83% were women and the median age was 58 years (Table 1). The median disease duration was 7.5 years. Most of the patients discontinued a TNFα-inhibitor (76%) and in 68% it was the first bDMARD the patients were ever treated with. The median observation time of all 318 patients was 2.8 years (IQR 1.2-4.9). In our cohort no patients had a disease duration shorter than 1.3 years and only a small number of patients (n=19) had a disease duration ≤ 2 years. At the moment of bDMARD withdrawal, 59% of patients had a concomitant treatment with methotrexate or leflunomide. 145 patients (46%) were treated with methotrexate and or leflunomide during the whole time of bDMARD-free remission, whereas 36% of the patients never received methotrexate or leflunomide during bDMARD free remission (Table 1).

Of the included patients 24% remained in remission, with a mean observation time of 2.1 years (SD 2.3) and a median observation time of 1.2 years (IQR 0.7; 2.9). 241 patients (76%) lost remission after bDMARD discontinuation during follow up. Of those 54% fulfilled the criteria of loss of remission by re-starting a bDMARD, 34% by experiencing a DAS28-ESR flare above 2.6 and 12% fulfilled both criteria. The median time in remission was 0.9 years (95%CI 0.7-1.0). Within the first year after bDMARD discontinuation already 54% of patients had lost remission. In 42% the same bDMARD was restarted.

Female patients lost remission faster than male patients (Figure 1A; HR 1.5, 95CI 1.1-2.1, p=0.005). This was also seen after adjusting for other covariates (Figure 2; HR 1.4, 95%CI 1.0-2.0, p=0.04). Age and ACPA or RF status had no impact on the time in bDMARD-free remission, neither in the univariate (Age: hazard ratio [HR] 1.00, 95%CI 1.0 – 1.0, p=0.76, ACPA: HR 1.19, 95%CI 0.9 – 1.6, p=0.26, RF: HR 1.04, 95%CI 0.8 – 1.4, p=0.77) nor in multivariate cox regression analyses (Figure 2). Also, smoking was not associated with a shorter time in remission in the univariate analysis (HR 0.96, 95%CI 0.8 – 1.2, p=0.7). We analyzed the association of disease duration with the time in remission in quartiles and found a significant correlation (1st quartile: disease duration ≤3.9yrs, 2nd quartile: >3.9 to ≤7.5yrs, 3rd quartile: >7.5 to ≤ 12.6yrs, 4th quartile: >12.6yrs). Longer disease duration was associated with a faster

loss of remission (Figure 1B; p=0.03. In univariate analysis HR[2nd quartile] 1.4, 95%CI 0.9-2.0, p=0.1, HR[3rd quartile] 1.7, 95%CI 1.2-2.5, p=0.005, HR[4th quartile] 1.5, 95%CI 1.1-2.2, p=0.03 *vs* 1st quartile). Also in multivariate analysis the inverse association of disease duration and time on remission was seen (Figure 2; HR[2nd quartile] 1.6, 95%CI 1.0 – 2.3, p=0.03, HR[3rd quartile] 1.7, 95%CI 1.1 – 2.4, p=0.01, HR[4th quartile] 1.5, 95%CI 1.0 – 2.3, p=0.05 *vs* 1st quartile).

In patients who were not in remission defined by the CDAI at baseline (CDAI ≤2.8), there was a tendency for a faster loss of remission (Figure 1C; univariate cox regression: HR [CDAI low disease activity = CDAI >2.8-10] 1.2, 95%CI 0.7-1.9, p=0.5, HR [CDAI moderate/high disease activity = CDAI >10] 1.3, 95%CI 0.7-2.5,p=0.4, both *vs* CDAI remission). This association became significant in multivariate analysis (HR [CDAI low disease activity] 1.6, 95%CI 1.1 – 2.4, p=0.02, HR [CDAI moderate/high disease activity] 2.4, 1.4 – 4.2, p=0.002, both *vs* CDAI remission; Figure 2). In the univariate regression there was no significant association between bDMARD-free remission and DAS28-ESR (HR 1.1, 95%CI 0.9 – 1.4, p=0.5), SDAI (HR 1.0, 95%CI 1.0 – 1.0, p=0.9), RADAI5 scores (HR 1.1, 95%CI 1.0 – 1.2, p=0.02) or HAQ (HR 1.2, 95%CI 0.9 – 1.6, p=0.1). The univariate regression analysis of the number of different bDMARD agents prior to the discontinuation of the bDMARD suggested an elevated risk to loose remission, after exposure to at least 3 prior bDMARDs (HR 1.8, 95%CI 1.0 – 3.1, p=0.051). In addition, therapy with tocilizumab, abatacept or tofacitinib as a group compared to TNFα-inhibitors showed a higher risk for loss of remission (HR 1.3, 95%CI 1.0-1.8, p=0.05), these trends however were not confirmed in multivariate analyses, neither for the numbers of bDMARDs before (Figure 2; HR 1.2, 95%CI 0.6 – 2.2, p=0.6) nor for bDMARD type (Figure 2; HR 1.1, 95%CI 0.8-1.5, p=0.7). No differences were found between tocilizumab (HR 1.1, 95%CI 0.7-1.7, p=0.6) and abatacept (HR 0.8, 95%CI 0.4-1.4, p=0.4) versus TNF-Inhibitors. Tofacitinib showed a significantly increased hazard ratio for loss of remission (HR 2.1, 95%CI 1.0-4.1, p=0.04). However the patient number, who were treated with tofacitinib was too small to draw any firm conclusions (n=14).

Patients who received methotrexate and or leflunomide during the observation period had a lower risk for loss of remission in the univariate analysis than those without csDMARD therapy (Figure 1D; HR 0.7, p=0.006). This was also significant in the multivariate analysis (Figure 2; HR 0.8, 95%CI 0.6 – 1.0, p=0.05).

The patients were included for analysis regardless of the reason to stop the bDMARD as long as patients fulfilled the criteria of remission as detailed above. The reason for discontinuation was available in the database for 286 patients (89.9%). For 48 of those patients ineffectiveness was indicated as one of the reasons for discontinuation of the bDMARD therapy (reasons for discontinuation are shown in Supplementary Table 1). To take into account the possibility of patients failing bDMARDs being misclassified as patients in remission, we performed a subgroup analysis in which we excluded the patients with ineffectiveness as reason of the bDMARD discontinuation (Supplementary Table 2). The results of this subgroup (n=270) were comparable, with the same parameters showing an association with the time in remission, except that there was no significant difference between patients with disease duration >13yrs (4^{th} quartile) and ≤4yrs (1^{st} quartile) in the multivariate analysis (Supplementary Figures S1, S2).

The results of the multivariable regression analyses shown in Figure 2 and supplementary Figure S2 are based on the imputed data, the respective results of a complete case analysis are shown in supplementary Figure S3.

Discussion

We have studied bDMARD free remission in patients who had stopped bDMARDs or tsDMARDs in the large prospective real-world cohort SCQM. In our cohort the large majority (76%) of the patients lost remission after a median of 9 months. However, 24% of the patients maintained remission with a median follow up of 1.2 years. This is less than reported in randomized controlled trials or observational studies (14-19). Tanaka et al reported in the HONOR study that 47% of the patients in

remission discontinuing infliximab remained in DAS28 remission at 12 months (19). In the PRIZE study the rate of patients in sustained remission at 24 and 39 weeks after discontinuation of etanercept was 40%, in patients who also discontinued therapy with methotrexate only 23% remained in remission (17). In a substudy of the BeSt study 52% of the patients remained in LDAS, in 48% therapy with infliximab had to be restarted after a median of 17 months (20). The randomized controlled trial RETRO reported similar numbers with 52% relapses within 12 months in a study arm with 6 months dose reduction of bDMARD and csDMARD followed by discontinuation of all DMARD therapy (21). The lower percentage of patients that remained in remission after bDMARD discontinuation found in our study may be due to the longer follow up. A recent observational study has shown that relapse rates after tapering biologics in a real-life setting increased over time after 12 months (22). In our study the mean disease duration was 7.5 years which is longer than in most of the trials published so far. In fact, disease duration was inversely correlated with the time in bDMARD free remission in our cohort. An association of successful cessation of TNF-inhibitor therapy with a shorter symptom duration until treatment start in RA patients has previously been shown in a small study (23). Similarly, in the HONOR study an association of longer disease duration with a loss of remission after discontinuation of adalimumab was shown (19). In addition, a disease duration of >10 years was reported to be associated with a shorter time to relapse in an open label randomized controlled trial of stopping vs continuing therapy with TNF-inhibitors (24).

Whereas DAS28 itself was not an independent predictor of maintenance of remission in our study, CDAI low, moderate or high disease activity as opposed to CDAI remission at the time of bMDARD discontinuation was significantly associated with a faster loss of remission. This result is in agreement with the HONOR study that reported “deep” remission with a DAS28<2.0 being a predictor for maintenance of remission (19). In the RETRO study DAS28 was predictive for remaining in remission, however in that study the median DAS28 at baseline was well below 2.0 (21). Our data suggest that the more stringent remission criteria defined by CDAI rather than DAS28 remission should be considered when assessing the risk of disease relapse after discontinuation of bDMARDs.

Another predictor for a shorter time in remission was the absence of a csDMARD therapy. Patients with either methotrexate or leflunomide therapy had a significantly higher chance to remain in remission. In the PRIZE study the remission rates in the patients in the methotrexate arm dropped significantly after discontinuation of methotrexate at week 39 (17). Similarly, in the RETRO study the relapse rates were the highest in the group that stopped all DMARD therapy (21). Our data supports to continue csDMARD therapy in patients that stop bDMARD therapy in sustained remission.

Function as assessed by HAQ was not found to be associated with time in bDMARD free remission in our study. In contrast, HAQ at baseline was reported to be associated with the risk of flares in a step down strategy of TNF inhibitor therapy (14). Low HAQ was also a predictor for restarting therapy in DMARD free remission in an exploratory analysis of the BeSt study (25). In addition, a Japanese study found that a lower HAQ-DI was a predictor for maintenance of remission or LDA after discontinuation of therapy with abatacept (26).

Dose reduction and discontinuation of bDMARD treatment has been studied for a variety of bDMARDs, including the TNF inhibitors etanercept, infliximab, adalimumab, certolizumab pegol as well as abatacept and tocilizumab (8). However, no direct comparisons have been published. In our analysis we did not observe significant differences of the time in bDMARD free remission between patients with previous TNF inhibitor therapy and patients with abatacept or tocilizumab treatment. Patients who discontinued the JAK inhibitor tofacitinib tended to have an increased hazard ratio for a shorter time in bDMARD free remission, however the patient number was too small to draw any conclusions. Further studies are needed with larger patient populations to analyse potential differences of the risk of losing remission for the individual bDMARDs. This is important as also the predictors for loss of remission may differ between different bDMARDs, e.g. in a recent study low IL-6 levels were shown to be associated with a loss of remission in patients discontinuing tocilizumab (27).

Interestingly, we found that female sex was significantly associated with a shorter time of bDMARD free remission, after adjusting for differences in baseline characteristics. A recent systematic literature review found 4 studies with baseline characteristics and information on successful or unsuccessful discontinuation of bDMARDs. Patients who did not relapse were more often female (9). However, there are no reports of gender as an independent predictor of successful bDMARD discontinuation.

The strengths of our study are the real-life setting, a relatively large number of patients and a longer follow up than most of the published randomized trials. Limitations are the observational nature of this prospective cohort study. The decision to stop bDMARD treatment was at the discretion of the treating rheumatologist, which could introduce an indication bias. Disease flares in between visits may have been missed, although this also applies to randomized studies.

In summary, our study provides information on predictors for successful discontinuation of bDMARD therapy in patients with RA in remission in a real-world setting. Our findings confirm and extend previous results from randomized controlled studies and suggest that bDMARD discontinuation should be considered primarily in patients with a disease duration <4 years, fulfilling CDAI remission criteria and continuing csDMARD therapy.

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Ethics:

All patients included in the SCQM registry have given written informed consent. The data was obtained in anonymized from from the SCQM database. The study was approved by the responsible ethics review board (EKNZ 2020-00018)

Disclosures: DK reports personal fees from Abbvie, Gilead, Lilly, Novartis and Pfizer, outside of the submitted work. UW reports personal fees from Abbvie, Bristol-Myers Squibb, Gilead, Lilly, Novartis, Pfizer and Roche outside of the submitted work.

Author contributions: DK and AS conceived the study. SA, VJ analysed the data. SA and DK wrote the manuscript. All authors reviewed the data and gave critical input.

Data availability statement: All data relevant to the study are included in the article or uploaded as supplementary information.

Table 1. Demographic and disease characteristics of patients with bDMARD-free remission at the time of bDMARD discontinuation

Characeristics			Median (IQR) or %
Sex	n=318	female	74
Age	n=318		57.5 (46.2-66.0)
Smoking	n=155	never	45
		former	26
		current	29
Disease duration in years	n=312		7.5 (3.9-12.6)
Type of bDMARD/tsDMARD	n=318	TNF-inhibitor	76
		Abatacept	6
		Tocilizumab	14
		Tofacitinib	4
Number of previous	n=318	0	68
bDMARDs		1 to 2	27
		≥3	5
Concomittant csDMARD	n=318		64
ACPA positive	n=261		64
RF positive	n=306		72
DAS28-ESR	n=318		2 (1.5-2.3)
CDAI	n=127		5 (2-9)
		remission	27
		low activity	54
		moderate activity	18
		high activity	1
SDAI	n=122		8 (5-13)
		remission	15
		low activity	51
		moderate activity	33
		high activity	1
RADAI5	n=219		2.4 (1.2-4)
HAQ	n=228		0.4 (0-1)

*at any time during bDMARD-free remission. ACPA: Anti citrullinated peptide/protein, bDMARD: biologic disease-modifying antirheumatic drug, CDAI: clinical disease activity index, DAS28-ESR: disease activity score 28, HAQ: The health assessment questionnaire, RADAI5: Rheumatoid disease activity index-5, RF: Rheumatoid factor, SDAI: simplified disease activity index, csDMARD: conventional disease-modifying antirheumatic drug

Figure legends

Figure 1: Kaplan-Meier curves for time in bDMARD-free remission according to different risk factors. Cumulative percentage of patients in bDMARD-free remission over time are shown according to sex (A), disease duration shown in quartiles (1st quartile: ≤3.9 years, 2nd quartile: >3.9 to ≤7.5 years, 3rd quartile >7.5 to ≤ 12.6 years, 4th quartile: >12.6 years) (B), CDAI Score (C) and concomitant csDMARD therapy during bDMARD-free remission (D).

Figure 2: Multivariate cox regression analysis with impact on time in bDMARD-free remission

[1]Disease duration in years, 2nd quartile (>3.9 to ≤7.5 years) vs 1st quartile (≤3.9 years, reference), [2]3rd quartile (>7.5 to ≤ 12.6 years) vs 1st quartile, [3]4th quartile (>12.6 years) vs 1st quartile, [4]vs. CDAI remission.

Abbreviations

ACPA	anti-citrullinated protein antibodies
bDMARD	biological disease-modyfinging antirheumatic drugs
CDAI	Clinical disease activity index
CI	Confidence Intervall
csDMARD	conventional synthetic disease-modifying antirheumatic drug
DAS28-ESR	Disease Activity Score 28
HAQ	Health Assessment Questionnaire
HR	Hazard Ratio
IQR	Interquartile range
RA	Rheumatoid Arthritis
RADAI5	rheumatoid arthritis disease activity index 5
RAU	Ratingen Score
RF	rheumatoid factor
SCQM	Swiss clinical quality management in rheumatic diseases registry
SDAI	Simple disease activity index

tsDMARD targeted synthetic disease-modifying antirheumatic drug

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Supplementary material

Supplementary Table 1. Reasons for discontinuation of the bDMARD as selected by the rheumatologists from the options: remission, ineffectiveness, adverse event, other.

Reason for bDMARD discontinuation	N (%)
Remission[1]	89 (28)
Ineffectiveness	48 (15)
Adverse event[2]	85 (27)
Other	64 (20)
Missing	32 (10)

[1] Including: remission, remission and other, remission and adverse event

[2] Including: adverse event, adverse event and other

Supplementary Table 2. Demographic and disease characteristics of patients with bDMARD-free remission at the time of bDMARD discontinuation (patients excluded with ineffectiveness as reason for discontinuation).

Characeristics			Median (IQR) or %
Sex	n=270	female	72
Age	n=270		58 (46-66)
Smoking	n=129	never	50
		former	25
		current	25
Disease duration in years	n=262		6.2 (3.4-11.5)
Type of bDMARD/tsDMARD	n=270	TNF-inhibitor	78
		Abatacept	4
		Tocilizumab	14
		Tofacitinib	4
Number of previous	n=270	0	69
bDMARDs		1 to 2	26
		≥3	5
Concomittant csDMARD	n=270		63
ACPA positive	n=222		64
RF positive	n=260		72
DAS28-ESR	n=270		1.9 (1.5-2.3
CDAI	n=103		4 (2-7
		remission	30
		low activity	56
		moderate activity	14
SDAI	n=100		8 (5-12)
		remission	16
		low activity	55
		moderate activity	28
		high activity	1
RADAI5	n=191		2 (1-3.6)
HAQ	n=192		0.4 (0-0.9)

Legends of supplementary Figures:

Supplementary Figure S1: Kaplan-Meier curves for time in bDMARD-free remission according to different risk factors (patients excluded with ineffectiveness as reason for discontinuation). Cumulative percentage of patients in bDMARD-free remission over time are shown according to sex (A), disease duration shown in quartiles (1st quartile: ≤3.9 years, 2nd quartile: >3.9 to ≤7.4 years, 3rd quartile >7.4 to ≤ 12.6 years, 4th quartile: >12.6 years) (B), CDAI Score (C) and concomitant csDMARD therapy during biologic-free remission (D).

Supplementary Figure S2: Multivariate cox regression analysis with impact on time in bDMARD-free remission (patients excluded with ineffectiveness as reason for discontinuation). [1]Disease duration in years**,** 2nd quartile (>3.9 to ≤7.5 years) vs. 1st quartile (≤3.9 years, reference), [2]3rd quartile (>7.4 to ≤ 12.6 years) vs. 1st quartile, [3]4th quartile (>12.6 years) vs. 1st quartile), [4]vs. CDAI remission, ACPA: Anti citrullinated protein antibodies, bDMARD: biological disease-modifying antirheumatic drug, CDAI: clinical disease activity index, DAS28-ESR: disease activity score 28, RF: Rheumatoid factor, csDMARD: conventional disease-modifying antirheumatic drug

Supplementary Figure S3: Multivariate cox regression analysis with impact on time in bDMARD-free remission. (complete case analysis). [1]Disease duration in years, 2nd quartile (>3.9 to ≤7.5 years) vs. 1st quartile (≤3.9 years, reference), [2]3rd quartile (>7.5 to ≤ 12.6 years) vs. 1st quartile, [3]4th quartile (>12.6 years) vs. 1st quartile, [4]vs. CDAI remission, ACPA: Anti citrullinated protein antibodies, bDMARD: biological disease-modifying antirheumatic drugs, CDAI: clinical disease activity index, DAS28-ESR: disease activity score 28, RF: Rheumatoid factor, csDMARD: conventional disease-modifying antirheumatic drug

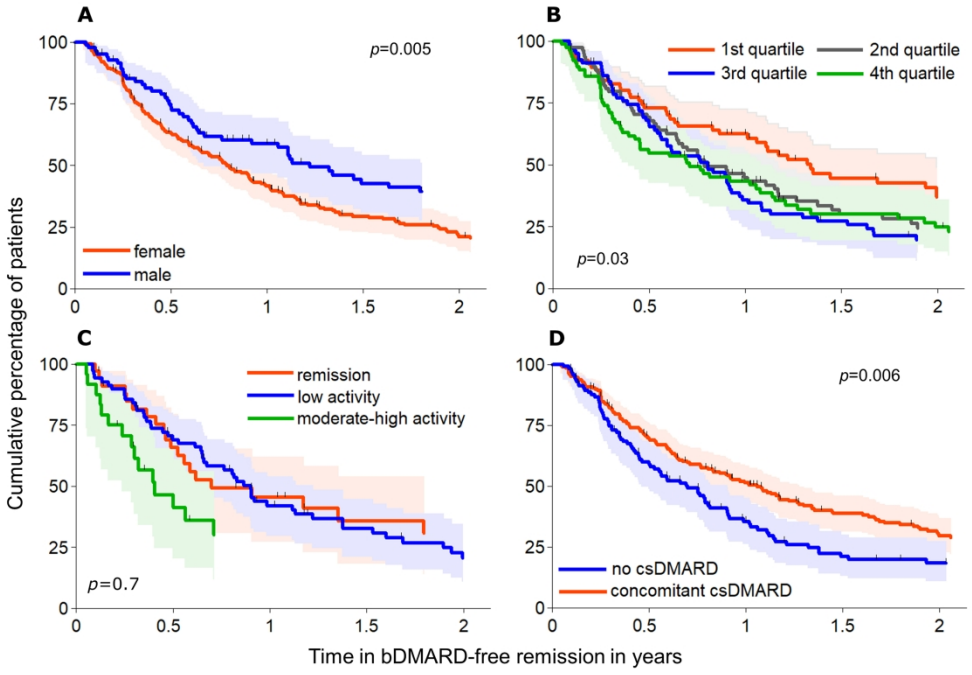

Figure 1

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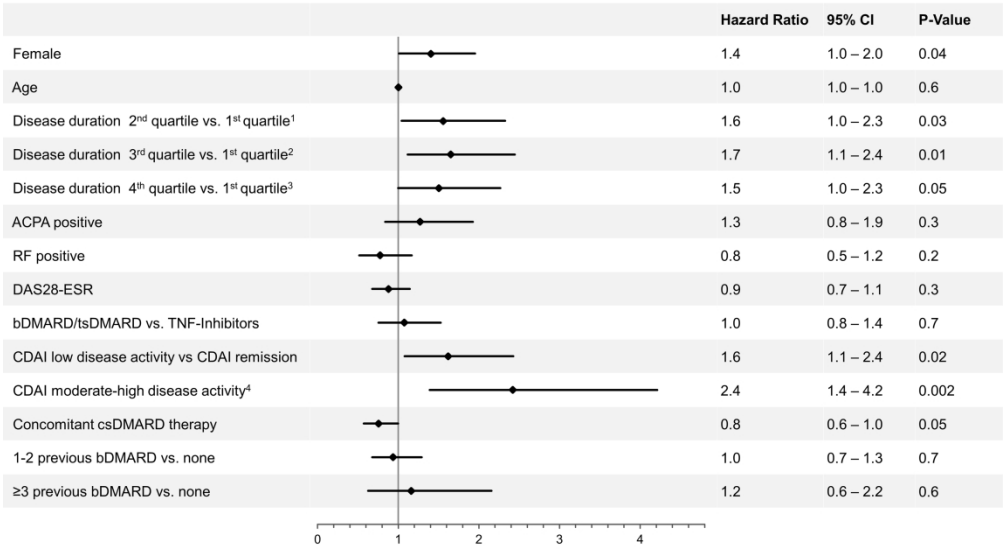

Figure 2

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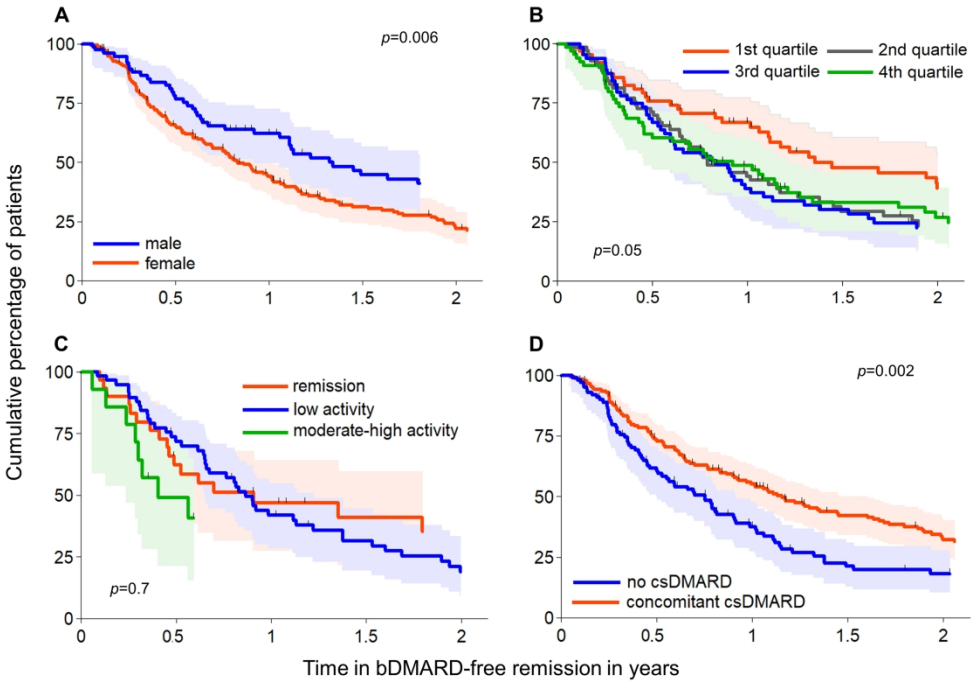

Figure S1

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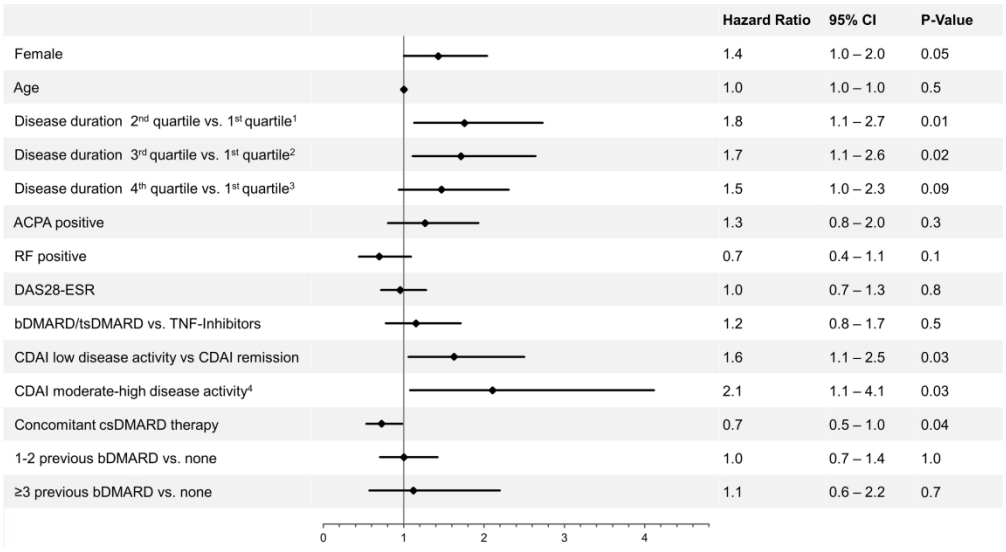

Figure S2

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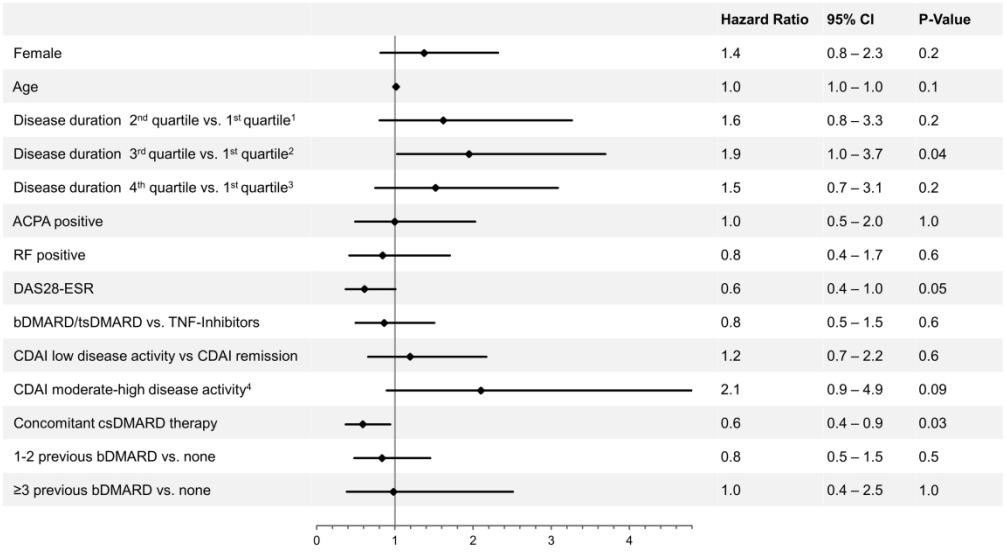

Figure S3

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